SUPPLEMENTARY FIGURES AND TABLES

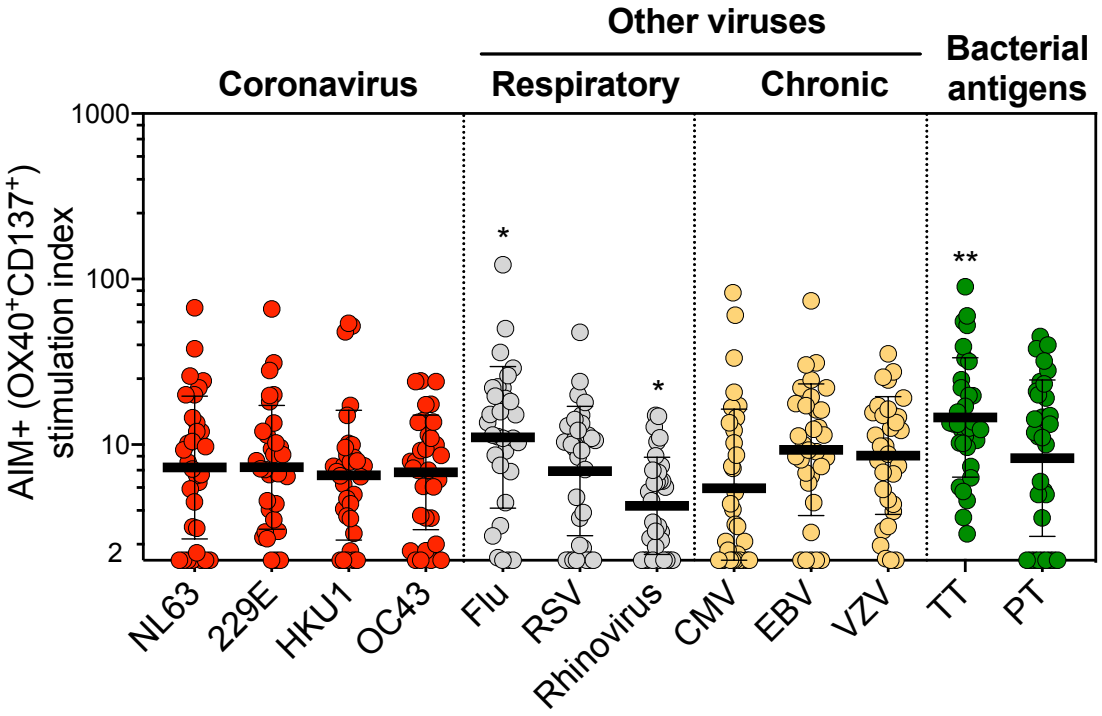

Fig. S1 Stimulation Index of CD4+ T cell responses to four representative CCC and other pathogens. Common cold coronavirus (CCC) and several other human pathogens-specific T cell responses were measured as percentage of AIM+ (OX40+CD137+) CD4+ T cells after stimulation of PBMCs with peptides pools. Graphs show individual response of four CCC (NL63, 229E, HKU1, and OC43) and other pathogens plotted as stimulation index (SI) against DMSO negative control. First time point of the longitudinal series is plotted (n = 32). Data are represented as geometric mean and SD. Kruskal-Wallis test adjusted with Dunn's test for multiple comparisons was performed and adjusted p values < 0.05 considered statistically significant. *, $p < 0.05$, **, $p < 0.01$.

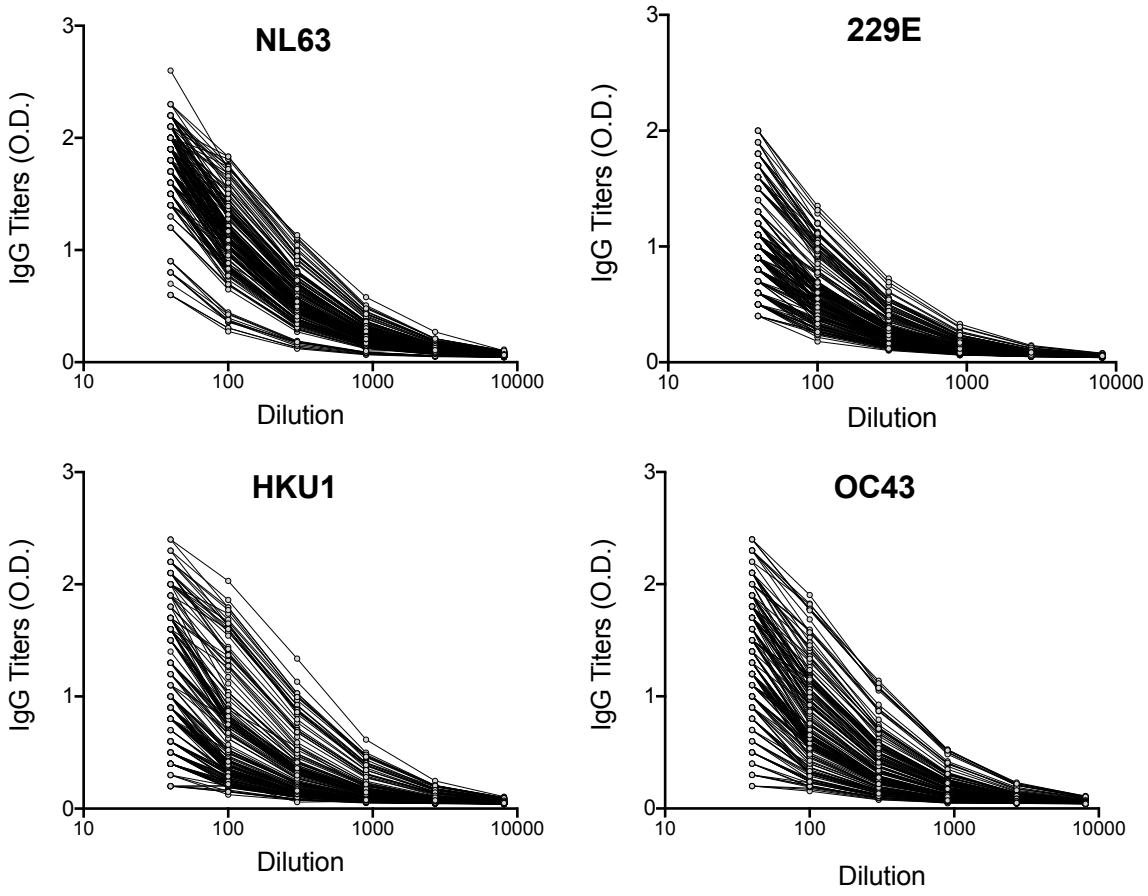

Fig. S2 IgG serial dilutions for endpoint titers and AUC calculation. Plasma ELISA IgG serial dilutions to calculate the area under the curve (AUC) for CCC viruses (229E, NL63, HKU,1 and OC43) spike receptor binding domain (RBD) protein are shown for the longitudinal cohort (n = 32).

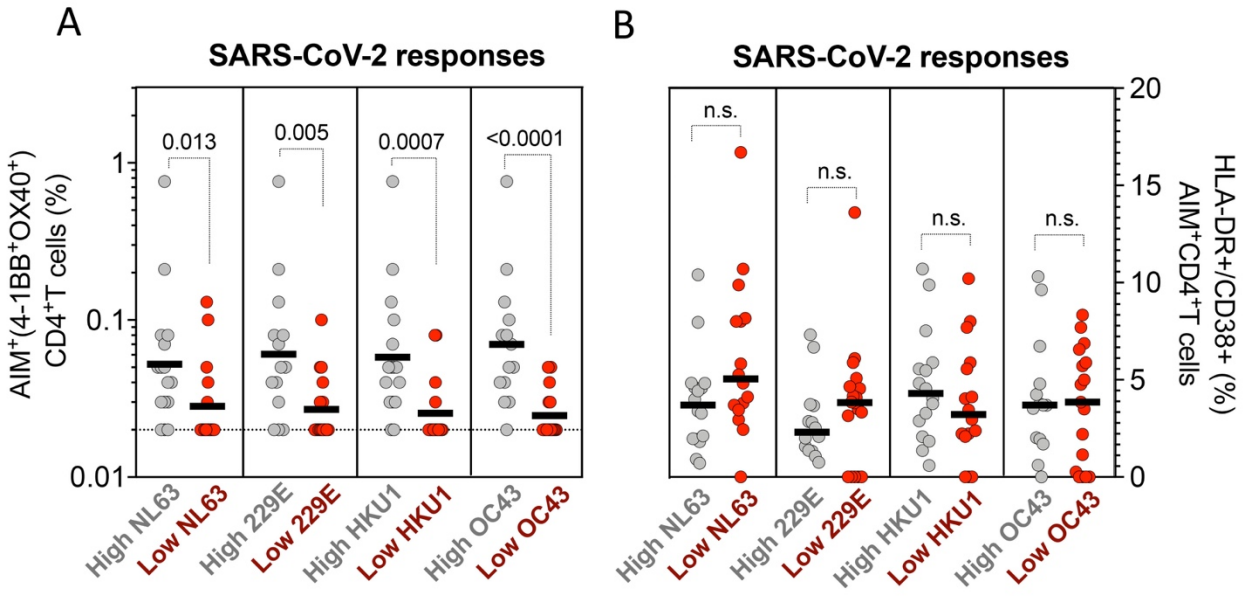

Fig. S3 High CD4+ T cell reactivity across all the CCC viruses is associated with high pre-existing SARS-CoV-2 immunity. (**A**) Antigen-specific T cell responses were measured as percentage of AIM+ (OX40+CD137+) CD4+ T cells after stimulation of PBMCs with peptides pools for CCC and SARS-CoV-2 (representing pre-existing immunity in pre-pandemic samples). (**B**) Recent activated CCC-specific T cell responses were measured by calculating the percent of HLA-DR^{+}CD38^{+} of AIM+ (OX40^{+}CD137^{+}) CD4+ T cells. Each dot represents the response of an individual subject (n=32) at first time point. Median is shown. High responders for each CCC are shown in gray, and low responders in red. The different SARS-CoV-2 specific immune responses between high and low CCC responders were compared using Mann-whitney test, and p values < 0.05 considered statistically significant.

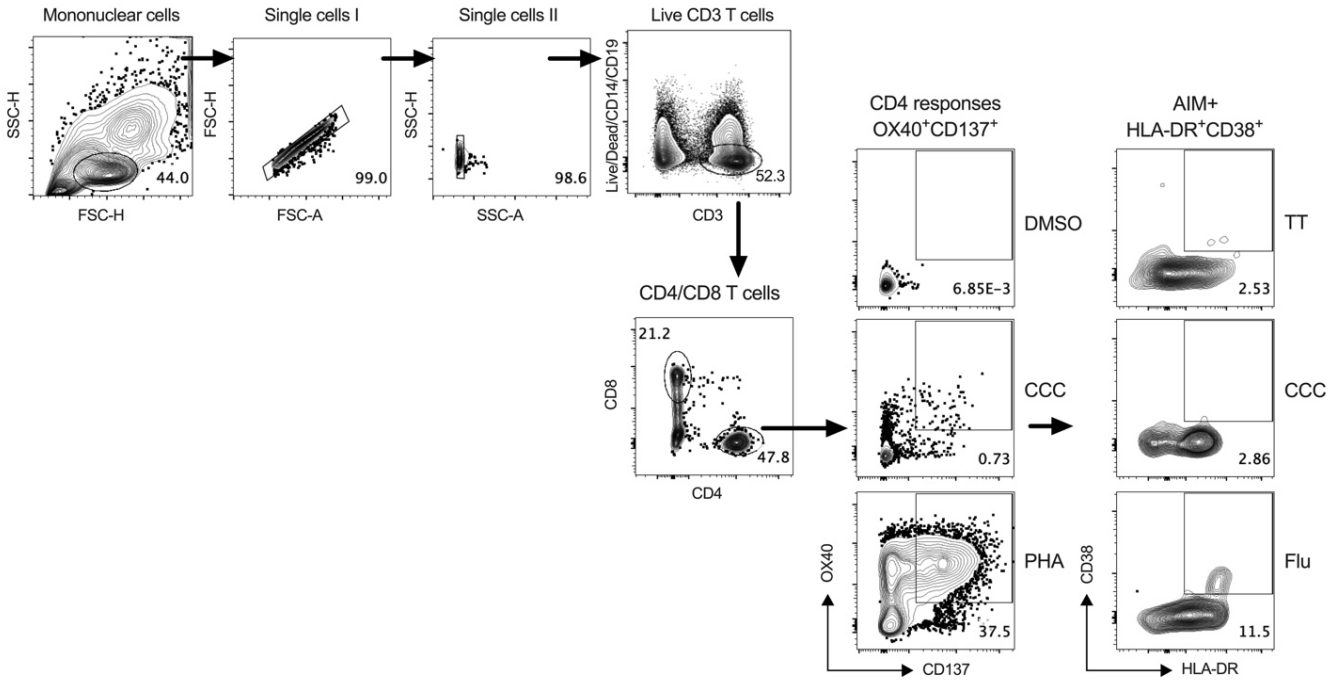

Fig. S4 Ilustrative flow cytometry gating strategy for the assessement of antigen-specific CD4+ T cell responses. Representative gating of reactive OX40+CD137+ CD4+ T cells (AIM+) from donor PBMCs is shown. Briefly, mononuclear cells were gated out of all events followed by subsequent singlet gating. Live CD3+ cells were gated as Live/Dead-CD14-CD19-CD3+. Cells were then gated as CD4+CD8-, and antigen-specific cells definied as OX40+CD137+ CD4+ T cells (AIM+) and after antigen stimulation, and frequencies calculated as percent of total CD4+ T cells. Representative AIM+ responses after stimulating with positive (PHA) or negative (DMSO) controls and CCC (OC43) specific megapools are presented on the right. Recently activated cells (HLA-DR+CD38+) were further gated from AIM+ cells. Representative plots are show for TT, CCC (OC43) and Flu.

Table S1. List of the antibodies used in this study

Antibody	Fluorochrome	Clone	Vendor	Catalog number
CD3	BV805	UCHT1	BD Biosciences	612895
CD4	BV605	RPA-T4	BD Biosciences	562658
CD8	BV496	RPA-T8	BD Biosciences	612942
CD14	V500	M5E2	BD Biosciences	561391
CD19	V500	HIB19	BD Biosciences	561121
CD137	APC	4B4-1	Biolegend	309810
OX40	PE-Cy7	Ber-ACT35	Biolegend	350012
CD69	PE	FN50	BD Biosciences	555531
HLA-DR	AF700	LN3	eBiosciences	56-9956-42
CD38	BV786	HIT2	BD Biosciences	563964
CD45RA	BV421	HI100	Biolegend	304130
CCR7	FITC	G043H7	Biolegend	353216
Live/Dead Viability	eF506/Aqua	-	eBiosciences	65-0866-18